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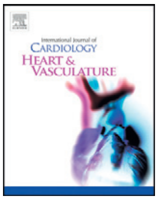

Non-invasive estimation of pulmonary outflow tract obstruction: A comparative study of cardiovascular phase contrast magnetic resonance and Doppler echocardiography versus cardiac catheterization

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ABSTRACT

Aim: To compare estimated pressure gradients from routine follow-up cardiovascular phase-contrast magnetic resonance (PC-MR) with those from Doppler echocardiography and invasive catheterization in patients with congenital heart disease (CHD) and pulmonary outflow tract obstruction.
Methods: In 75 patients with pulmonary outflow tract obstruction maximal and mean PC-MR gradients were compared to maximal and mean Doppler gradients. Additionally, in a subgroup of 31 patients maximal and mean PC-MR and Doppler pressure gradients were compared to catheter peak-to-peak pressure gradients (PPG).
Results: Maximal and mean PC-MR gradients underestimated pulmonary outflow tract obstruction as compared to Doppler (max gradient: bias = +8.4 mm Hg (+47.6%), $r = 0.89$, $p < 0.001$; mean gradient: +4.3 mm Hg (+49.0%), $r = 0.88$, $p < 0.001$). However, in comparison to catheter PPG, maximal PC-MR gradients (bias = +1.8 mm Hg (+8.8%), $r = 0.90$, $p = 0.14$) and mean Doppler gradients (bias = −2.3 mm Hg (−11.2%), $r = 0.87$, $p = 0.17$) revealed best agreement. Mean PC-MR gradients underestimated (bias = −7.7 mm Hg (−55.6%), $r = 0.90$, $p < 0.001$) while maximal Doppler gradients systematically overestimated catheter PPG (bias = +13.9 mm Hg (+56.5%), $r = 0.88$, $p < 0.001$).
Conclusions: Estimated maximal PC-MR pressure gradients from routine CHD follow-up agree well with invasively assessed peak-to-peak pressure gradients. Estimated maximal Doppler pressure gradients tend to overestimate, while Doppler mean gradients agree better with catheter PPG. Therefore, our data provide reasonable arguments to either apply maximal PC-MR gradients or mean Doppler gradients to non-invasively evaluate the severity of pulmonary outflow tract obstruction in the follow-up of CHD.

1. Introduction

In many patients with congenital heart disease (CHD), the assessment of the severity of pulmonary outflow tract obstruction is crucial. Historically, the catheter peak-to-peak pressure gradient (PPG) has been used as the diagnostic gold standard to evaluate the degree of pulmonary outflow tract obstruction and was employed to decide when to intervene. In todays clinical routine transthoracic echocardiography is generally decisive. The estimated maximal instantaneous Doppler gradient is the non-invasive diagnostic method of choice to define when an intervention is indicated [1,2]. Cardiovascular magnetic resonance (CMR) imaging has become a non-invasive imaging standard in the follow-up of repaired CHD [3,4]. CMR examinations in CHD typically include phase-contrast flow quantification (PC-MR) of large intrathoracic vessels e.g. to determine the degree of pulmonary regurgitation [5,6]. Patients with repaired CHD often develop combined pulmonary regurgitation and pulmonary outflow tract obstruction. While the measurement of pulmonary flow is potentially an unrivalled strength of conventional PC-MR, limitations to accurately assess peak flow velocities are present [7,8]. However, peak flow velocities are provided in

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every case of pulmonary PC-MR flow quantification, but it remains unclear how to deal with the existing data at the present time. Recent studies have shown that estimated maximal instantaneous Doppler gradients overstate catheter PPG [9,10]. Since it is known that PC-MR underestimates peak flow velocities when compared to Doppler echocardiography [11], we hypothesised that estimated maximal pressure gradients from PC-MR agree closer with catheter PPG. Therefore, the purpose of the present study was to compare estimated pressure gradients from routine follow-up cardiovascular PC-MR with those from Doppler echocardiography and invasive catheterization in CHD with pulmonary outflow tract obstruction.

2. Methods

2.1. Study subjects

Patients with CHD who underwent transthoracic Doppler echocardiography and cardiovascular PC-MR of the pulmonary outflow tract were identified by search of the local radiological-cardiovascular database. Patients with pulmonary outflow tract obstruction were included for analysis if they had Doppler (estimated maximal Doppler gradient of 6 mm Hg or higher) and cardiovascular PC-MR examination within 4 month. Additionally, a subgroup analysis of patients was performed who underwent Doppler, PC-MR as well as cardiac catheterization within 4 month. For patients with multiple Doppler examinations during these periods, the study with the lowest time delay to either PC-MR or catheterization was chosen. All examinations were clinically indicated and the results were compared retrospectively. Written informed consent could not be obtained from participants for their clinical records to be used in the study. Accordingly, data were analysed anonymously to protect their identities. The study was approved by the Institutional Review Board at the University of Göttingen Medical Centre and complies with the Declaration of Helsinki.

2.2. Doppler echocardiography

Pulmonary outflow tract maximal and mean pressure gradients were estimated using continuous wave (CW) Doppler. Echocardiography examinations were performed on iE33 ultrasound systems (Philips Healthcare, Leiden, The Netherlands) using Philips S5-1 ultrasound probes (Nyquist limit 61, gain 50%). CW Doppler measurements (frequency 1.8 MHz, angle 0 to 20°) of the pulmonary outflow tract were performed in multiple standardized views [12]. Digital offline analysis (2D Cardiac Performance Analysis, TomTec Imaging System, Munich, Germany) of the digitally recorded Doppler-data was performed to determine peak flow velocities. The heartbeat with the highest velocity detected in any imaging window was included in the analysis. A region of interest (ROI) was drawn around the systolic Doppler signal to determine the peak and the mean flow velocity (= time averaged peak flow velocity across the systolic signal) (Fig. 1). Maximal and mean Doppler gradients were estimated using the Bernoulli equation [13] $\Delta P = 4 (V)^2$, where ΔP is the maximal or mean pressure gradient and V the peak or mean flow velocity.

2.3. Phase-contrast magnetic resonance

MR flow quantification was performed on 1.5 T (Symphony Syngo B17, Siemens Healthcare, Erlangen, Germany) using a retrospective ECG gated cine phase-contrast sequence in breath-holding technique with the following imaging parameters: spatial resolution $1.7 \times 1.7 \times 5.5$ mm^3, TE/TR 3.2/75.4, flip angle 30°, encoding velocity 130–450 cm s^{-1}, 20 phases. If patients were not able to follow respiratory instructions, a free breathing retrospective ECG gated cine phase-contrast technique was used alternatively with the following imaging parameters: spatial resolution $1.3 \times 1.3 \times 5.0$ mm^3, TE/TR 3.0/27.0, flip angle 30°, encoding velocity 130–430 cm s^{-1}, 30 phases. Pulmonary outflow tract blood flow was measured through plane in an imaging plane as recommended for pulmonary flow quantification in the follow-up of CHD [14,15]. Magnitude and phase-contrast maps were analysed using commercially available software (QFlow, Medis, Leiden, The Netherlands). ROIs were drawn on each of the 30 frames (free-breathing technique) or 20 frames (breath-hold technique) around the circumference of the main pulmonary artery to determine the pixel encoding of the peak flow velocity in each frame (Fig. 2). The peak flow velocity from each frame was exported to a spreadsheet to generate peak flow velocity versus time curves (Fig. 1). The peak flow velocity versus time curve was used to identify the overall peak flow velocity (= peak of all systolic frames) and to calculate the mean flow velocity (= time averaged peak flow velocity of all systolic frames). Maximal and mean PC-MR pressure gradient were estimated according to the Bernoulli equation as described above for Doppler measurements.

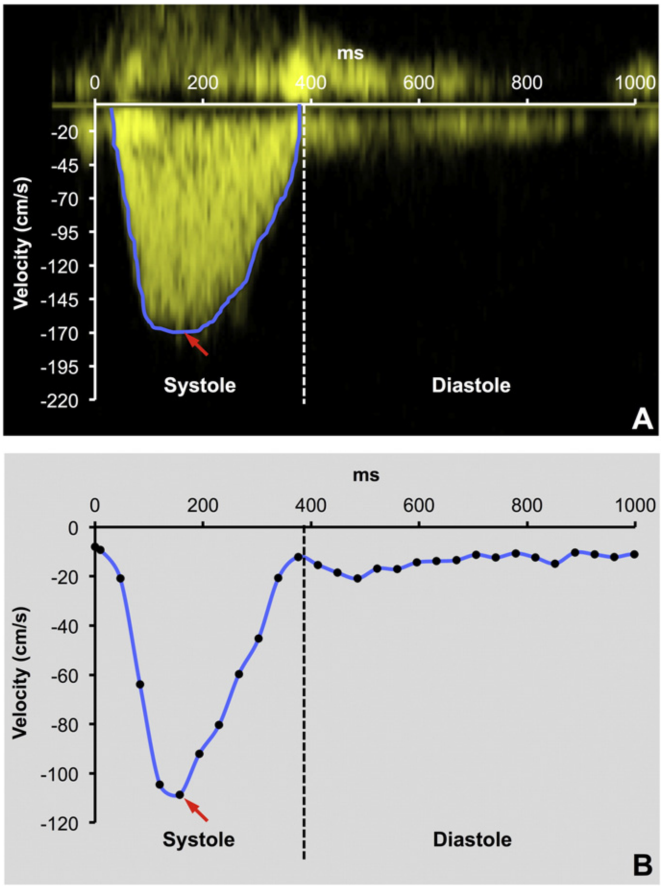

Fig. 1. Peak velocity versus time curves. Peak velocity versus time curves for (A) Doppler echocardiography and (B) phase-contrast magnetic resonance (PC-MR) acquisitions were used to identify the peak flow velocity (red arrow) and to calculate the mean flow velocity (time averaged peak flow velocity).

2.4. Cardiac catheterization

Non-invasively estimated pressure gradients were compared to the catheter peak-to-peak systolic pressure gradient (PPG). All patients underwent catheterization under conscious sedation. Invasive pressure measurements were performed with fluid-filled catheters. PPG were measured using the non-simultaneous pullback technique. The PPG was defined as the difference between the peak ventricular and peak pulmonary arterial pressure.

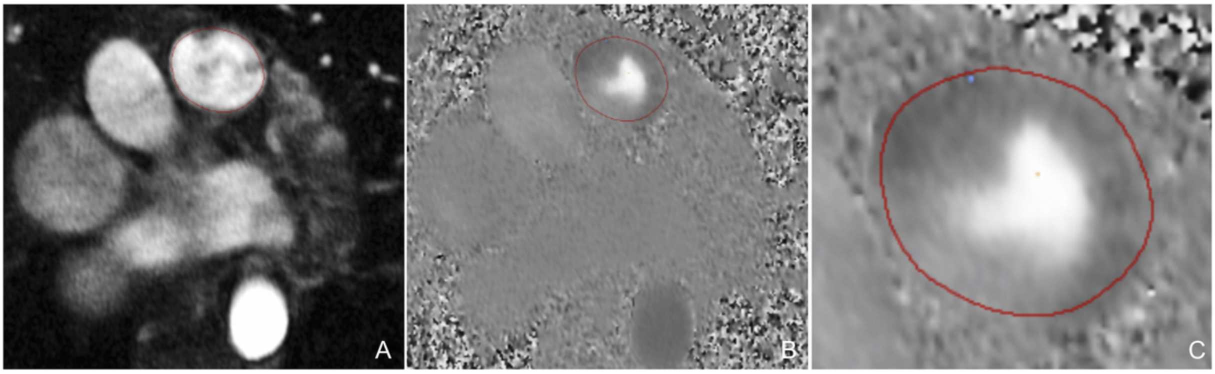

Fig. 2. PC-MR quantification of peak flow velocities. Magnitude image (A) with corresponding phase map (B) are shown. A region of interest (red contour) was drawn around the circumference of the main pulmonary artery in one image with subsequent propagation to all images. The pixel encoding for the peak flow velocity is indicated in orange (C).

2.5. Statistical analysis

Statistical analysis was performed using Microsoft Excel and IBM SPSS Version 22 for Macintosh. Estimated pressure gradients from PC-MR, Doppler echocardiography and catheterization were compared by calculating the relative mean differences with 95% limits of agreement (±2 standard deviations) according to the method of Bland and Altman with absolute values and as a percentage [16]. Bivariate correlation was performed to estimate Pearson's correlation coefficients. After logarithmic transformation of the sample, pressure gradients were compared using a paired *t*-test. The Shapiro–Wilk test was applied to test normal distribution. All p-values <0.05 were considered statistically significant.

Intra-observer and inter-observer variability of maximal and mean PC-MR and Doppler gradient measurements were assessed in 7 randomly selected subjects. Two independent experienced observers who were blinded to each other's findings analysed the PC-MR and digitally recorded Doppler data. One of the two observers reanalysed the results after an interval of 1 month. Intra-observer and inter-observer variability were assessed by Bland–Altman analysis.

3. Results

Data of 75 patients who underwent PC-MR and Doppler examinations as well as data of 31 patients with all three examinations (PC-MR, Doppler and cardiac catheterization) who met the inclusion criteria for the study were analysed. The median time delay between Doppler and PC-MR examination was 30 days (range: 0–114 days). In the subgroup of patients with catheter examination ($n = 31$) the median time delay between all three examinations (Doppler, PC-MR and cardiac catheterization) was 55 days (range: 2–123 days). Patient characteristics and primary cardiac diagnoses are summarized in Table 1.

Table 1
Patient characteristics.

	Doppler vs. PC-MR	Doppler, PC-MR vs. PPG
n	75	31
Age (range), years	27 ± 13 (1–58)	26 ± 13 (6–52)
Gender, male/female	40/35	15/16
Diagnosis		
Tetralogy of Fallot	34	16
Pulmonary valve stenosis	15	4
Status after Ross operation	8	3
Ebstein's anomaly	6	1
TGA	5	3
Common arterial trunk	3	3
Aortic coarctation	2	-
Double-outlet right ventricle	1	-
ASD	1	1

Data are expresses as mean ± standard deviation or as numbers.
PC-MR, phase contrast magnetic resonance; PPG, catheter peak-to-peak gradient; TGA, transposition of the great arteries; ASD, atrial septal defect; RV, right ventricle.

3.1. Doppler echocardiography versus phase-contrast magnetic resonance

PC-MR measurements were performed during breath-hold in 51 patients and during free breathing in 24 patients. The relationship between PC-MR and Doppler derived gradients followed the same pattern in both groups. Maximal PC-MR pressure gradients underestimated maximal Doppler gradients (bias = 8.4 mm Hg, 47.6%; limits of agreement: −8.9 to 25.7 mm Hg; $p < 0.001$; $r = 0.89$). Mean PC-MR underestimated mean Doppler pressure gradients likewise (bias = 4.3 mm Hg, 49.0%; limits of agreement: −4.9 to 13.5 mm Hg; $p < 0.001$; $r = 0.88$) (Fig. 3, Table 2).

3.2. Phase contrast magnetic resonance versus catheterization

Estimated maximal PC-MR pressure gradients and catheter PPG revealed good agreement (bias = 1.8 mm Hg, 8.8%; limits of agreement: −10.3 to 13.9 mm Hg; $p = 0.14$; $r = 0.90$). In contrast, estimated mean PC-MR pressure gradients underestimated catheter PPG (bias = −7.7 mm Hg, −55.6%; limits of agreement: −18.5 to 3.2 mm Hg; $p < 0.001$; $r = 0.90$) (Fig. 4, Table 3).

3.3. Doppler echocardiography versus catheterization

Estimated mean Doppler pressure gradients and catheter PPG revealed good agreement (bias = −2.3 mm Hg, 11.2%; limits of agreement: −13.9 to 9.1 mm Hg; $p = 0.17$; $r = 0.87$). In contrast, estimated maximal Doppler gradients overestimated catheter PPG (bias = 13.9 mm Hg, 56.5%; limits of agreement: −8.5 to 11.4 mm Hg; $p < 0.001$; $r = 0.88$) (Fig. 5, Table 3).

3.4. Reproducibility

The intra-observer reproducibility of estimated maximal, mean PC-MR gradients and estimated maximal, mean Doppler gradients was 0.2 mm Hg (limits of agreement: −0.8 to 1.2 mm Hg), 0.6 mm Hg (limits of agreement: −0.7 to 1.9) and −1.9 mm Hg (limits of agreement: −1.6 to 1.2), −2.3 mm Hg (limits of agreements: −0.7 to 0.6 mm Hg), respectively. Corresponding inter-observer reproducibility was 0.1 mm Hg (limits of agreement: −1.3 to 1.5 mm Hg), 0.3 mm Hg (limits of agreement: −1.4 to 1.9 mm Hg) and −1.0 mm Hg (limits of agreement: −3.0 to 1.0 mm Hg), −0.2 mm Hg (limits of agreement: −1.8 to 1.4 mm Hg).

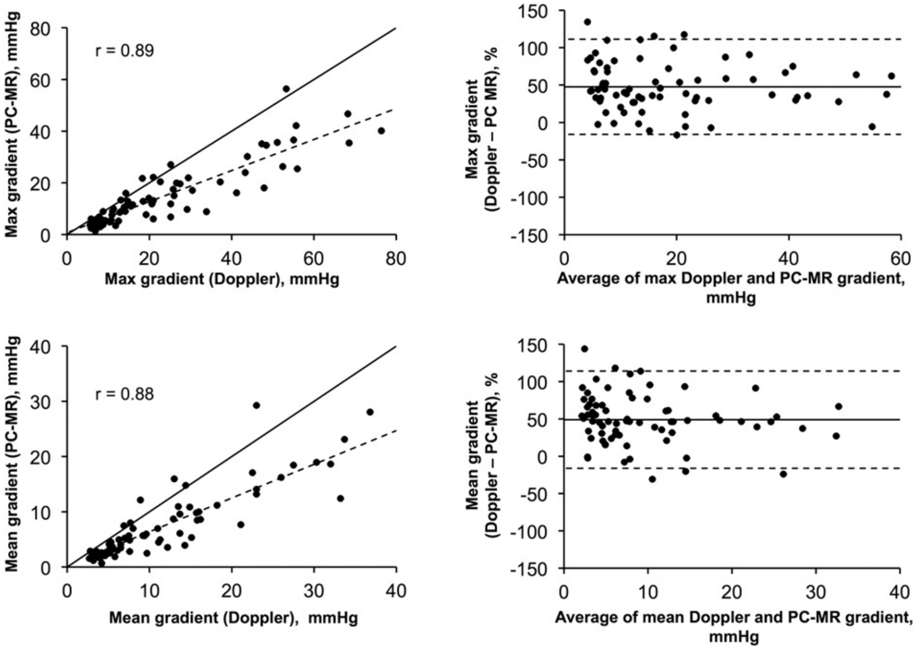

Fig. 3. PC-MR vs. Doppler pressure gradients. Pearson correlation (left) of maximal Doppler and PC-MR (upper panel) and mean Doppler and PC-MR pressure gradients (lower panel). Solid line represents the line of equality, dashed line the line of best fit. Corresponding Bland–Altman analysis (right) of Doppler and PC-MR gradients. Solid line represents the bias (mean difference), dashed lines limits of agreement (±2 standard deviation).

4. Discussion

We performed a comparative study of Doppler echocardiography, PC-MR and cardiac catheterization to evaluate the degree of pulmonary outflow tract obstruction in patients with CHD who were referred to routine CMR follow-up. Our data indicate that — with respect to the corresponding application of maximal or mean pressure gradients — both Doppler echocardiography and PC-MR have the potential to estimate the severity of pulmonary outflow tract obstruction in routine follow-up of CHD non-invasively. We found that estimated maximal PC-MR pressure gradients and estimated mean Doppler gradients agree well with catheter PPG.

In the present study, we aimed to compare clinically available techniques for the estimation of outpatient pressure gradients. PC-MR is known to underestimate peak flow velocities when compared to Doppler echocardiography, which is most likely due to intravoxel averaging of phase [15,17]. Our data confirm a mean difference of peak and mean flow velocities between both modalities of about 0.5 m s^{-1} and 0.3 m s^{-1}, respectively. The problem of intravoxel averaging led to the development of Fourier Velocity Encoding (FVE) techniques, which allow acquiring a velocity spectrum of each image pixel resulting in a more precise evaluation of peak flow velocities using PC-MR [18,19]. However, FVE has not found widespread implementation into clinical routine so far, since practical obstacles, e.g. the need for long breath hold periods during the acquisition limit its clinical applicability particularly in patients who are not able to follow breathing instructions (e.g. paediatric patients with CHD).

Previous simultaneous Doppler-catheter measurements indicated good agreement between estimated maximal CW Doppler gradients and catheter PPG [20,21]. However, more recent data suggest that catheter PPG agree best with estimated mean Doppler (and not peak instantaneous Doppler) gradients and that estimated peak instantaneous Doppler gradients systematically overestimate catheter PPG by slightly more than 20 mm Hg [9,10], as emphasized in the current ACC/AHA guidelines for the management of adults with CHD [22]. Our results can confirm the proposed relationships between Doppler derived pressure gradients and catheter PPG as described by Silvilairat et al. [9,10]. Moreover, our study demonstrated that estimated maximal PC-MR pressure gradients from routine follow-up agree closely with catheter PPG. In the present study, we employed maximal instantaneous pressure gradients from Doppler echocardiography and PC-MR as calculated by the Bernoulli equation using peak flow velocities. Catheterization on the other hand provides peak-to-peak pressure gradients, which are by definition lower than catheter peak instantaneous gradients [23]. Thus, the good agreement between catheter PPG and maximal PC-MR as well as catheter PPG and mean Doppler gradients is possibly due to both being underestimates of the catheter instantaneous pressure gradient. However, most of the outcome data and particularly current recommendations for surgical intervention or balloon valvuloplasty in paediatric and adult patients with CHD and pulmonary outflow tract obstruction are related to catheter PPG [1,2]. Clinically relevant pulmonary outflow tract obstruction amenable to pulmonary balloon valvuloplasty is defined as a resting catheter PPG or an outpatient peak instantaneous

Table 2
Gradient data, correlation and agreement between estimated PC-MR and Doppler gradients (n = 75).

	Median (mm Hg)	Range (mm Hg)	Correlation coefficient (r)	Bias ± SD (mm Hg)[a]	Bias ± SD (%)[a]	*t*-Test (p-value)
Doppler max	23	6–76	–	–	–	–
PC-MR max	14	1–56	0.89[b]	+8.4 ± 8.8[b]	+47.6[b]	$p < 0.001$[b]
Doppler mean	12	3–44	–	–	–	–
PC-MR mean	7	1–29	0.88[c]	+4.3 ± 4.7[c]	+49.0[c]	$p < 0.001$[c]

SD, standard deviation; other abbreviations as in Table 1.

[a] Calculated: Doppler − PC-MR.

[b] As compared to Doppler max.

[c] As compared to Doppler mean.

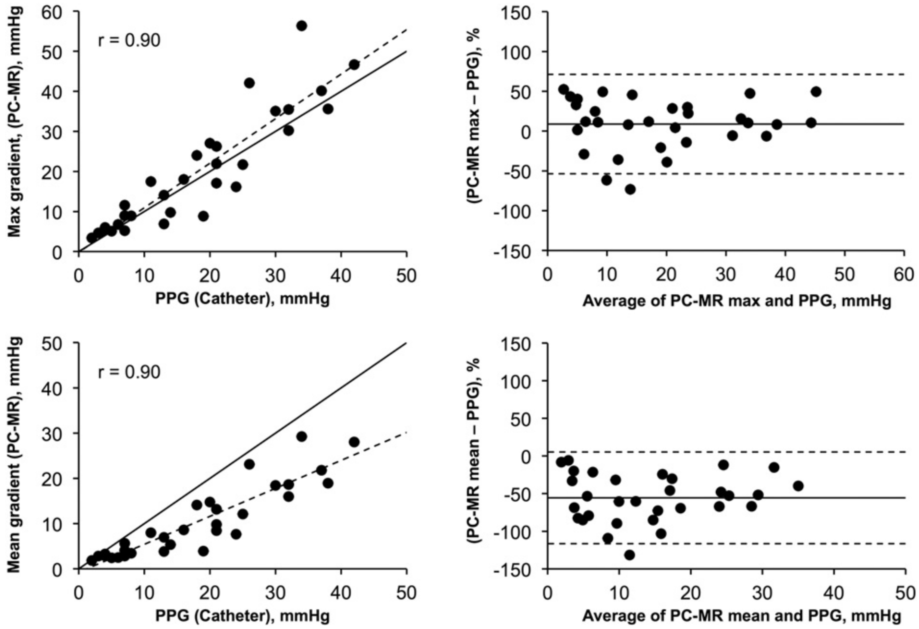

Fig. 4. PC-MR vs. catheter peak-to-peak pressure gradients. Pearson correlation (left) of maximal (upper panel) and mean (lower panel) PC-MR pressure gradients vs. catheter peak-to-peak pressure gradients. (PPG) Solid line represents the line of equality, dashed line the line of best fit. Corresponding Bland–Altman analysis (right) of maximal and mean PC-MR gradients vs. catheter PPG. Solid line represents the bias (mean difference), dashed lines limits of agreement (±2 standard deviation).

Doppler gradient ≥40 mm Hg [1,2]. In the present study, 12 patients revealed a maximal Doppler gradient ≥40 mm Hg in their precatheterization echocardiographic examination. The following catheterization confirmed a gradient ≥40 mm Hg in only one of them. This emphasizes a potential risk of misleading and unnecessary indications for balloon valvuloplasty when estimated peak instantaneous pressure gradients from Doppler echocardiography are used to evaluate the severity of pulmonary outflow tract obstruction non-invasively. Precatheterization PC-MR revealed a maximal gradient ≥40 mm Hg in only 4 patients and was confirmed by the following catheterization in one of them. This also exemplifies the need for reliable and robust non-invasive methods to assess pulmonary outflow tract obstruction pressure gradients in order to avoid unnecessary catheterization and ionizing radiation.

On the basis of our study we therefore propose to either apply the estimated mean Doppler (and not peak instantaneous Doppler) gradient or the estimated maximal PC-MR (and not mean PC-MR) pressure gradient to evaluate pressure gradients from invasive peak-to-peak catheterization. We have selected inclusion criteria of a peak pulmonary outflow tract gradient of ≥6 mm Hg (maximal CW Doppler gradient) to ensure the inclusion of patients with low (i.e. before catheterization is indicated) and higher pressure gradients (i.e. indication for catheterization). This spectrum corresponds to patients with CHD and pulmonary outflow tract obstruction who are typically referred to CMR follow-up. Our results show that the relationship between PC-MR, Doppler and catheter PPG is valid in both low-gradient and medium- to high-gradient conditions.

4.1. Limitations

The following limitations need to be addressed. Firstly, we did not analyse the impact of conscious sedation. All patients underwent cardiac catheterization in conscious sedation while PC-MR and Doppler echocardiography were performed without sedation. However, indications for cardiac catheterization and intervention in paediatric cardiac disease are based on pressure gradients assessed with the patient sedated in the catheterization laboratory and non-sedated during non-invasive evaluation, respectively [2]. Secondly, approximately one fourth of patients underwent PC-MR during free-breathing conditions while the remaining PC-MR measurements were performed during a breath-hold, which might impact peak flow quantification. The study sample was too small to perform a quantitative comparison, however, we could confirm that the relationship between PC-MR and Doppler derived pressure gradients followed the same pattern in both groups. Thirdly, patients with highly severe outflow tract obstruction could not be included. Future studies will need to address whether the relationship between CMR, Doppler and catheterization derived pressure gradients holds true for highly obstructive conditions. Fourthly, pressure gradient data from Doppler, CMR and cardiac catheterization were acquired non-simultaneously. Future investigations need to focus on simultaneous comparative studies, which might be possible by using robust real-time flow CMR quantification [24] in combination with invasive pressure monitoring [25]. Finally, the study's data were taken from routine clinical examinations; therefore it might be limited

Table 3
Gradient data, correlation and agreement between catheter peak-to-peak pressure gradients and estimated gradients from PC-MR and Doppler echocardiography ($n = 31$).

	Median (mm Hg)	Range (mm Hg)	Correlation coefficient (r)[a]	Bias ± SD (mm Hg)[a,b]	Bias (%)[a,b]	*t*-Test (p-value)[a]
Catheter PPG	18	2–42	–	–	–	–
PC-MR max	20	3–56	0.90	+1.8 ± 6	+8.8	0.14
PC-MR mean	10	2–29	0.90	−7.7 ± 6	−55.6	$p < 0.001$
Doppler max	32	6–76	0.88	+13.9 ± 11	+56.5	$p < 0.001$
Doppler mean	16	3–44	0.87	−2.3 ± 6	−11.2	0.17

PPG, peak-to-peak pressure gradient; other abbreviations as in Tables 1 and 2.

[a] As compared to Catheter PPG.

[b] Calculated: PC-MR or Doppler pressure gradient — Catheter PPG.

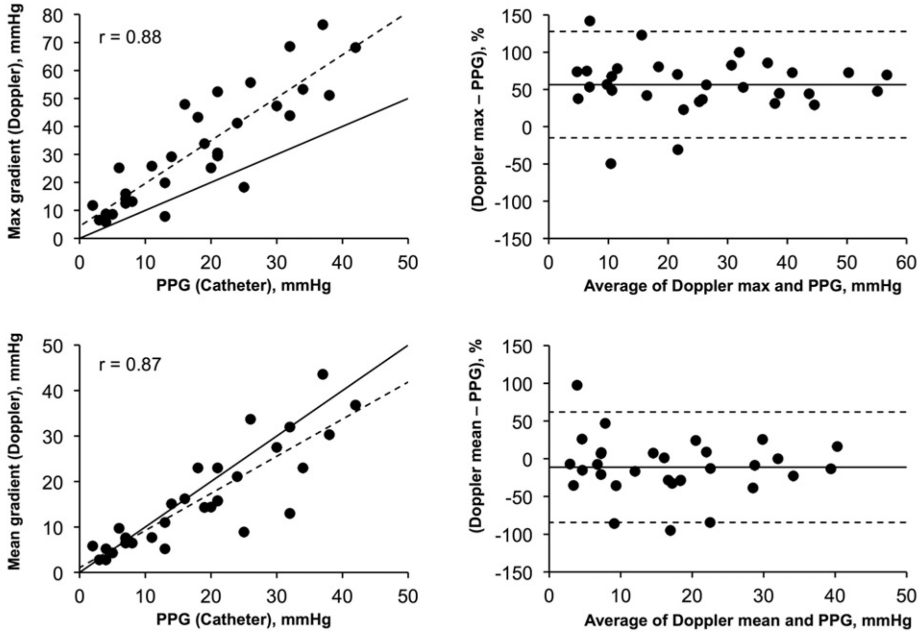

Fig. 5. Doppler vs. catheter peak-to-peak pressure gradients. Pearson correlation (left) of maximal (upper panel) and mean (lower panel) Doppler pressure gradients vs. catheter peak-to-peak pressure gradients (PPG). Solid line represents the line of equality, dashed line the line of best fit. Corresponding Bland–Altman analysis (right) of maximal and mean Doppler gradients vs. catheter PPG. Solid line represents the bias (mean difference), dashed lines limits of agreement (±2 standard deviation).

due to its retrospective character. Accordingly, the proposed relationships between non-invasively estimated and invasively quantified pressure gradients will need to be verified in future prospective clinical studies.

5. Conclusions

Estimated maximal PC-MR and Doppler mean pressure gradients agree well with invasively assessed catheter PPG in patients with CHD with pulmonary outflow tract obstruction. In contrast, estimated maximal Doppler pressure gradients tend to overestimate catheter PPG. Since recommendations for surgical intervention or balloon valvuloplasty are based on catheter PPG in this patient group, the results of our study provide reasonable arguments to either apply estimated maximal PC-MR gradients or estimated mean Doppler gradients to evaluate the severity of pulmonary outflow tract obstruction in the follow-up of CHD non-invasively. The proposed findings will need to be verified in future prospective clinical studies.

Grants

None.

Conflicts of interest

None.

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